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CT characteristics of pheochromocytoma – Relevance for the evaluation of adrenal incidentaloma

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Background: Up to 7% of all adrenal incidentalomas (AIs) are pheochromocytomas (PCCs). In the evaluation of AI, it is generally recommended to exclude PCC by measurement plasma free or 24h urinary fractionated metanephrines. However, recent studies suggest to abstain from biochemical exclusion of PCC in cases of lesions with computed tomography (CT) characteristics of an adrenocortical adenoma (ACA).
Aim: To determine the proportion of PCCs with ACA-like attenuation or contrast washout on CT.
Methods: For this multicenter retrospective study, two central investigators independently analyzed the CT reports of 533 patients with 548 histologically confirmed PCCs. Data on tumor size, unenhanced Hounsfield Units (HU), absolute percentage washout (APW) and relative percentage washout (RPW) were collected besides clinical parameters.
Results: Among the 376 PCCs for which unenhanced attenuation data were available, 374 had an attenuation of >10 HU (99.5%). In the two exceptions (0,5%), unenhanced attenuation was exactly 10 HU, which lies just within the range of ≤10 HU that would suggest a diagnosis of ACA. Of 76 PCCs with unenhanced HU >10 and available washout data, 22 (28,9%) had a high APW and/or RPW, suggestive of ACA.
Conclusion: Based on the lack of PCCs with an unenhanced attenuation of <10 HU, and the low proportion (0,5%) of PCCs with an attenuation of =10 HU, it seems reasonable to abstain from biochemical testing for PCC in AIs with an unenhanced attenuation ≤10 HU. The assessment of contrast washout, however, is unreliable to rule out PCC.

This retrospective study examines the CT characteristics of 548 pheochromocytomas (PCCs). The findings suggest to avoid biochemical testing for PCC in incidentalomas with unenhanced attenuation ≤10HU.

Introduction

Adrenal pheochromocytomas (PCCs) and extra-adrenal sympathetic paragangliomas are rare tumors that arise from catecholamine producing chromaffin cells [1]. Up to 40% of chromaffin tumors are associated with hereditable tumor syndromes [2-5]. The most accurate diagnostic test for the biochemical diagnosis of these tumors is the measurement of plasma free or 24h urinary fractionated metanephrines [6,7]. Typical symptoms and signs include headache, tremors, palpitations, sweating, and anxiety. However, in up to 25% of patients signs and symptoms are lacking and up to 30% of PCCs are diagnosed following the discovery of an adrenal incidentaloma (AI) [7,8].

The prevalence of AI on thoracic, abdominal and pelvic computed tomography (CT) ranges between 1.0% and 8.7% depending on age [9-14]. The majority of AIs are adrenocortical adenoma (ACA) [12]. Less prevalent causes are myelolipomas, cysts, adrenocortical carcinoma and metastases from other malignancies. PCCs account for up to 7% of AIs [7]. In contrast to situations when significant adrenal hormone secretion or malignancy are suspected, no treatment is indicated for benign non-functioning ACA. In 2016, the European Society of Endocrinology (ESE) in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT) published a guideline to provide clinicians with evidence-based recommendations for clinical management of patients with AIs [7]. This guideline adapts a generally accepted approach in the evaluation of AI by taking into account quantitative CT characteristics. Either an attenuation of ≤10 Hounsfield Units (HU) on an unenhanced CT, or an absolute percentage washout (APW) ≥60% or a relative percentage washout (RPW) ≥40%

on a CT with delayed washout after 10-15 min are considered suggestive of ACA. However, the guidelines and an accompanied meta-analysis [15] clearly indicated that the unenhanced CT is the only reliable method to differentiate benign from malignant adrenal tumors. In addition, it was recommended to perform an endocrine work-up for AI, including the measurement of plasma free or 24h urinary fractionated metanephrines. However, it was also discussed that it could be reasonable to avoid biochemical testing for PCC in patients AI with a unenhanced attenuation of ≤10 HU. Nevertheless, the authors acknowledged that only two small studies were published on this topic [16,17]. The findings in the latter studies require confirmation in a larger number of patients before substantiated statements can be made. It is important to note that PCCs demonstrating an attenuation ≤10 HU have been described in literature, though very uncommonly [18,19]. Hence, in this international multicenter study we retrospectively evaluated the quantitative CT characteristics of PCCs, as indicated in the radiological reports, to assess the proportion and associated characteristics of PCCs with an ACA-like attenuation on CT scan, taking into account both unenhanced attenuation and contrast washout measurements.

Methods

Patients

We included patients with a histologically proven PCC (single or multiple) who had undergone a pre-operative CT scan, *i.e.* either unenhanced CT (+/- contrast enhanced CT) or contrast washout CT. Patients with post-contrast CT scan only were not eligible for inclusion. Patients had been diagnosed and treated in centers affiliated to ENSAT. Participating ENSAT centers were Mayo Clinic (n=153), Rochester, USA; Radboud University Medical Center, Nijmegen, The Netherlands (n=46); University Hospital Center Zagreb, Zagreb, Croatia (n=43); Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (n=42); Medical University of Warsaw, Warsaw, Poland (n=33); CHU de Bordeaux, Pessac, France (n=29); University Medical Center Groningen, Groningen, The Netherlands (n= 28); University Hospital of Florence, Florence, Italy (n=21); University of Birmingham, Birmingham, United Kingdom (n=20); Center hospitalier de l'Université de Montréal, Montreal, Canada (n=19); Hospices Civils de Lyon, Lyon, France (n=17); University Hospital of Wuerzburg, Wuerzburg, Germany (n=17); University Hospital of Krakow, Krakow, Poland (n=16); Cambridge University Hospitals, Cambridge, United Kingdom (n=12); Endocrinology in Charlottenburg, Berlin, Germany (n=12); Center Hospitalier Universitaire de Liege, Liege, Belgium (n=10); Medizinische Klinik und Poliklinik IV Ludwig-Maximilians-Universität München, Munich, Germany (n=10); Hospital General Universitario de Albacete, Albacete, Spain (n=5). Patients provided informed consent, either under ENSAT or local institutional protocol, when required. Two hundred fourteen patients from the two Dutch centers were also included in a previous study on this topic by Buitenwerf et al.[20]. In the latter study, a central re-evaluation of CT images was performed to calculate unenhanced attenuation, whereas in the current study, both unenhanced attenuation and contrast washout were analyzed based on locally generated CT reports. Additional inclusion criteria were age at diagnosis ≥18 years, a diagnosis in or after the year 2000, availability of the CT report and clinical annotations (age, sex, underlying hereditary syndrome).

Biochemical testing and imaging

Biochemical testing, usually by measurement of plasma free or 24h urinary fractionated metanephrines, was performed according to local protocols with corresponding reference values. If metanephrines were not available, 24h urine or plasma catecholamines were utilized, in order of preference. Biochemical phenotypes were categorized as “adrenergic”,

"noradrenergic" or "normal". The phenotype was classified as "adrenergic" when the increment of metanephrines, relative to the upper limits of normal, exceeded 5% of the combined metanephrine and normetanephrine increments. Patients in whom these criteria were not fulfilled and in whom normetanephrine levels exceeded the upper limits of normal were classified as "noradrenergic" [21]. In addition, CT scans were performed according to local protocols regarding contrast procedure, acquisition and reconstruction parameters and approach to draw the region of interest for HU measurements.

Evaluation of CT reports

Anonymized imaging reports of pre-operative CT scans, generated by local radiologists as part of routine diagnostic evaluation, were submitted for central analysis. The reports were evaluated and scored independently by two observers (LC; JVH) who were blinded to the clinical information. Type of CT scan and field of view, number and location of lesions, tumor size, unenhanced HU, APW and RPW were considered. In case multiple unenhanced HU values were mentioned, the highest value was chosen for analysis. When in the local report values for APW/RPW were not mentioned, APW and RPW were calculated according to the formulas below, provided that the required parameters were available.

$$\text{APW} = \frac{HU\ portal\ venous\ phase - HU\ delayed\ phase}{HU\ portal\ venous\ phase - HU\ unenhanced} x100\%$$

$$\text{RPW} = \frac{HU\ portal\ venous\ phase - HU\ delayed\ phase}{HU\ portal\ venous\ phase} x100\%$$

PCCs were classified as ACA-like based on quantitative CT characteristics in case one of the following criteria were fulfilled: 1. Attenuation on unenhanced CT $\leq$10 HU or 2. Attenuation on unenhanced CT $\geq$10 HU and APW $\geq$60% and/or RPW $\geq$40%.

Data management and statistical analysis

Statistical analysis was performed with SPSS 17.0 for Windows. Clinical characteristics were compared between PCC patients with and without an ACA-like attenuation based on quantitative criteria. Characteristics were compared using an unpaired T test if variables were continuous or a Chi square test if variables were categorical. A two-sided P value of <0.05 was considered statistically significant.

Results

In total, 1011 cases of PCCs and extra adrenal sympathetic paragangliomas were screened for eligibility by the local investigators at the 18 participating centers. Four hundred and seven cases were excluded, mainly because of the performance of post-contrast CT only (n=305). After central review, 71 additional cases were excluded based on a diagnosis of extra-adrenal paraganglioma rather than PCC (n=25), lack of CT report (n=21), incomplete CT report (n=14), age <18 years (n=5), lack of histological proof of PCC (n=4) and performance of post-contrast CT only (n=2). Out of the remaining 533 patients with 548 histologically confirmed PCCs, quantitative CT characteristics were available in 368 patients with 382 PCCs (376 unenhanced HU +/- washout and 6 washout only). The clinical characteristics and information regarding HU and maximun diameter of PCCs are given in Table 1. The distribution of unenhanced attenuation (HU) is reported in Figure 1. Details on CT scan protocols and availability of quantitative data from radiology reports are given in Table 2.

PCCs with ACA-like attenuation or washout

Among the 376 PCCs for which unenhanced attenuation was available, 374 had an attenuation of >10 HU (99.5%, Figure 2). In the two exceptions (0,5%), unenhanced

attenuation was exactly 10 HU, which lies just within the range of ≤10 HU that would suggest a diagnosis of ACA (supplemental Table 1 [22]). Of these two PCCs, the histology reports were re-evaluated. The first lesion was a 42 mm right adrenal PCC with extensive central haemorrhage. Pre-operative urine catecholamine values were reported to be in the normal range, however, metanephrines were not measured. The second lesion was a 48 mm left adrenal PCC contained areas of prominent nodular adrenocortical hyperplasia besides PCC. No information on the biochemical phenotype could be retrieved.

Of 76 PCCs with unenhanced HU >10 and available washout, 22 (28,9%) had an APW ≥60% and/or an RPW ≥40%, suggestive of ACA. In one additional PCC APW/RPW was high as well, but unenhanced attenuation was unavailable. The local radiologists reported on six additional lesions with characteristics of ACA. The reasons for this, however, could not be verified, since washout data were unavailable and in the two cases where unenhanced attenuation was mentioned, it was >10 HU.

The PCCs with an unenhanced attenuation of >10 HU and high APW and/or RPW (n=22) did not differ from those with an unenhanced attenuation of >10 HU and low washout (n=54) with respect to sex, tumor size and hereditary syndrome (data not shown).

Two hundred eighty-two out of 548 PCCs (51.4%) were initially discovered as AI in 276 patients. One out of 199 lesions (lesion 1 in supplemental Table 1) with available quantitative data was among the two lesions of 10 HU. In this subgroup, out of 29 PCCs with unenhanced HU >10 and available washout, 10 (34.4%) had a high APW and/or RPW.

Discussion

We retrospectively evaluated the CT characteristics of PCC in the largest international cohort to date. Our main goal was to determine the proportion of PCCs with an ACA-like appearance based on either a low unenhanced attenuation or a high contrast washout. The analysis was based on locally generated radiological reports. Unenhanced HU values were available for 376 out of 548 histologically confirmed PCCs, two of which (0,5%) exhibited an attenuation of exactly 10 HU, consistent with an ACA-like attenuation according to recent ESE/ENS@T guidelines. In addition, among 76 PCCs with unenhanced HU >10 and available washout, 22 (28,9%) showed a high APW and/or RPW, wrongfully suggestive of ACA.

In 2016 ESE/ENSAT provided clinical practice guidelines for the management of patients affected by AIs. It was recommended that, as part of the endocrine workup, PCC should be excluded by measurement of plasma free or 24h urinary fractionated metanephrines in all AIs. However, it was discussed that an exception could be made for those cases where a non-contrast-enhanced CT attenuation was ≤10 HU. A disclaimer was made that the evidence to support this exception was very low, referring to two studies that showed a low likelihood of a PCC among adrenal lesions that are radiologically suggestive of ACA [16,17]. Sane et al. [16] examined whether PCC could be ruled out as cause of AIs on the basis of unenhanced attenuation values only. A cohort of 174 patients with AI was evaluated retrospectively. Unenhanced attenuation was available for 115 tumors. Nine patients had a PCC and in none of these tumors the unenhanced HU was below 10. They concluded that routine measurement of metanephrines is unnecessary in an asymptomatic patient with AI, provided that the lesion is of low attenuation, small and homogenous. Schalin-Jantti et al. [17] performed a 5-year prospective follow-up study of 56 patients with 69 lipid-rich (*i.e.* low attenuation) AIs, showing that 24h urinary metanephrines were normal at baseline as well as during follow-up. In addition, Jun et al. [19] studied 251 patients with AI and had similar results, leading to the conclusion that for small lesions (AI size ≤3 cm) non-contrast CT can substitute for biochemical testing for PCC. Nevertheless, all of the conclusions and recommendations made

in these previous studies are based on small subsets of PCCs among cohorts of patients with AIs.

Rather than taking AI as a starting point, in the present study and in one previous report, primarily patients with PCC were selected. Buitenwerf et al. [20] recently conducted a retrospective study including 214 patients affected by 222 histologically proven PCCs. Two expert radiologists re-evaluated the CT scan images independently. Only one PCC out of 222 demonstrated an attenuation value of <10 HU. This was a rare case of ACTH-dependent Cushing disease caused by a PCC. In the current study we found a similarly low proportion (0,5%) of PCCs with an unenhanced attenuation of ≤10 HU. In fact in none of the PCCs the unenhanced attenuation was below 10 HU and in only two PCCs it was exactly 10 HU. In these two cases, histology possibly provided some explanation. Hemorrhage, necrosis and additional adrenocortical [23] changes may result in intralesional heterogeneity, emphasizing the importance of selecting the proper region of interest for the assessment of attenuation.

In ~70% of AIs attenuation values are ≤10 HU, illustrating the large number of patients that might benefit from implementing radiological selection to determine in which patients biochemical screening is needed as second line test to rule out PCC [15]. Approximately 2000 patients with adrenal incidentaloma and attenuation value ≤10 HU would need to be biochemically screened in order to diagnose one case of PCC, assuming a 7% prevalence of PCC in the AI population, 70% frequency of attenuation ≤10 HU and a false-negative rate of 0.5% of radiological classification as determined in the present study (2857 AIs in total, including 2000 AIs ≤10 HU (70% of 2857) and 200 PCCs (7% of 2857), of which 1 (0.5% of 200) is missclassified by CT). In our opinion, this observation justifies omitting biochemical screening in low-attenuation AIs in order to prevent false-positive test results and unnecessary costs. In the given example of 2000 low attenuation AIs, based on 50 USD costs of metanephines measurement, omitting biochemical testing would result in an immediate cost reduction of 100.000 USD. In the context of a specificity of plasma metanephrines of ~80-90% [1], the true cost reduction is expected to be (much) higher when taking into account follow-up investigations prompted by false-positive biochemical testing results that could have been prevented.

Besides unenhanced HU, contrast washout rates are routinely used for the evaluation of adrenal lesions. The majority of ACA with an unenhanced HU >10 exhibit a high washout. Conversely, a high washout does not rule out PCC. We found that in almost one third of PCCs with available APW/RPW data, washout was high. This is in line with a previously meta-analysis of ten studies by Woo et al. [24]. They reported a rate of PCCs with a high washout pattern of 35%. Washout data for AI should therefore not be used to determine whether biochemical testing should be done or not.

There are several limitations to this study. This is a retrospective study of locally generated radiology reports coming from different centers using different CT machines, settings and contrast protocols. Drawing of the region of interest for the calculation of radiodensity was done at the discretion of the local radiologist. The impact of these potential confounders, however, is probably limited, inducing minimal variations in attenuation, estimated at 1-2 HU [20, 25]. In addition, many cases were excluded because of the availability of post-contrast CT scans only. The detail to which different quantitative parameters were reported varied considerably, leading to many missing data. On the other hand, the data were extracted directly from clinical practice, representative for 'real life'.

Conclusion

Based on the lack of PCCs with an unenhanced attenuation of <10 HU, and the low proportion (0,5%) of PCCs with an attenuation of =10 HU, it seems reasonable to abstain

from biochemical testing for PCC in AIs with an unenhanced attenuation ≤10 HU. The assessment of contrast washout, however, is unreliable to rule out PCC.

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The author reports no conflicts of interest in this work.

Notes

Abbreviations: ACA, adenoma; Ais, adrenal incidentalomas; APW, absolute percentage washout; CT, computed tomography; CTTA, CT texture analysis; ESE, European Society of Endocrinology; HU, Hounsfield units; lp-ACA, lipid-poor adenoma; MRI magnetic resonance imaging; PCCs, pheochromocytomas; RPW, relative percentage washout.

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Figure 1: Distribution of unenhanced attenuation (HU, Box whiskers plot). HU, Hounsfield Units

Figure 2: CT characteristics of PCCs. NA, not available; high washout, absolute ≥60% and/or relative ≥40%; low washout, absolute <60% and/or relative <40%.

Table 1: Characteristics of patients (n=368) and lesions (n=382) of whom quantitative CT characteristics were available

Sex: male (%)	163 (44,2%)
Age at diagnosis: mean±SD (y)	54,01± 15,05
Biochemical phenotype: n (%)	
Adrenergic	200 (54,3%)
Noradrenergic	111 (30,1%)
Normal values	18 (4,8%)
Unknown	39 (10,5%)
Hereditary syndrome: n (%)	60 (16,3%) *
Maximum diameter: mean±SD (mm)	42.73±21.96 (n= 306)
Unenhanced attenuation mean±SD (HU)	35.04± 10.95 (n= 375)

* RET (n=32), VHL (n=11), NF1 (n=11), SDHB (n=2), SDHD (n=2), MAX (n=1) and SDHAF2 (n=1)

Table 2: CT protocols and availability of quantitative data from radiological reports for PCCs

			CT scan protocol, nr %)			
			Unenhanced	**Unenhanced and post-contrast**	**Contrast washout**	**Unknown**
			94 (17,2)	**117 (21,4)**	**148 (27,0)**	**189 (34,5)**
Availability of quantitative data, n (%)	**Unenhanced HU only**	**298 (54,4)**	55 (58,5)	40 (34,2)	24 (16,2)	179 (94,7)
	Unenhanced HU and APW/RPW	**78 (14,2)**			77 (52,0)	1 (0,5)
	APW/RPW only	**6 (1,1)**			6 (4,1)	
	None	**166 (30,3)**	39 (41,5)	77 (65,8)	41(27,7)	9 (4,8)

HU, Hounsfield Units; AWP, absolute percentage washout; RWP, relative percentage washout